Comprehensive assessment of risk factors for the birth of a newborn with a congenital heart defect

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Abstract. The study aimed to identify risk factors and assess their contribution to the formation of congenital heart defects in newborns. 374 newborn children were examined, who were divided into groups II: Group I consisted of 324 newborns with congenital heart disease, group II consisted of 50 newborns without congenital heart disease. To determine the significance of risk factors, a questionnaire was compiled with a codifier of 42 signs reflecting socio-hygienic, medical and biological factors, the presence of intrauterine infections and the mother's medication intake during pregnancy and obstetric and gynaecological history. The questionnaire was filled out by the mothers of the examined newborns. The studies were conducted using: an epidemiological study of risk factors, an analysis of information content on relative risk – RR and the calculation of the odds ratio – OR. The results of the studies showed that the modifying risk factors for the development of congenital heart defects (CHD) in newborns are: the age of the mother over 35 years (OR 2.57), closely related (OR 4.69) and unregistered marriage (OR 4.48), the presence of CHD in the family (OR 7.70), severe anaemia (OR 3.65), acute upper respiratory tract infections during pregnancy (OR 3.98), herpetic viral infection (OR 48.8), taking antifungal drugs (OR 3.24), the presence of miscarriages (OR 8,11), the threat of termination (OR 5,12) and induced pregnancy (OR 5,68), severe toxicosis (OR 3,49), fetal hypoxia (OR 4.01) and stress during pregnancy (OR 7.50). Thus, when assessing the risk of developing congenital heart defects in newborns, the use of the modifying factors identified by us will allow planning methods of prevention in families at high risk of the disease.

1 Introduction

Currently, CHD and diseases of the cardiovascular system occupy a dominant place in terms of prevalence in comparison with other malformations in children and remain the leading cause of their death, accounting for about 50% of all causes of death from malformations [17]. The mortality rate in CHD is extremely high, by the end of the 1st week, 29% of newborns die, by the 1st month-42%, by the 1st year-87% of children [3].

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Further improvement of medical care for CHD in newborns should be carried out by creating a specialized cardiological system, including improving prenatal/postnatal diagnostic methods. Knowledge of the mechanisms of the formation of CHD and diseases of the cardiovascular system, in the intrauterine period in the fetus, allows timely diagnosis of diseases and qualified conservative and surgical measures [1].

The currently projected increase in the prevalence of CHD is undoubtedly due to the improvement of existing and the emergence of new diagnostic methods, improving the quality of imaging technical methods, improving the quality of training and qualification of specialists [19].

In recent years, cardiac surgery begins in the neonatal period and is provided to 2-2. 5 thousand newborns [2].

Timely prenatal and early neonatal diagnostics of congenital heart pathology, along with optimal medical and surgical care, allows to significantly minimize the complications of the disease in a newborn after birth.

Currently, the incidence of CHD does not decrease, which dictates the identification of risk factors for congenital heart defects for the development of new ways and approaches to prevent the disease [11].

It is generally accepted that three factors are of primary importance in the formation of congenital heart defects: hereditary predisposition, the adverse influence of environmental factors and the combined effect of these environmental factors with genotypic heredity [5].

The solution of this urgent problem requires further research in order to obtain complete information about the causes that affect the occurrence and formation of such a formidable disease.

The aim is to identify risk factors and assess their contribution to the formation of congenital heart defects in newborns.

2 Materials and methods

The paper presents the results of examinations for 374 newborn children who were on inpatient treatment in neonatal intensive care units, neonatal pathology and outpatient examination in the Regional Children's Multidisciplinary Medical Center of Samarkand in the period from 2018 to 2020, which were divided into groups II:

Group I consisted of 324 newborns with congenital heart disease.

Group II consisted of 50 newborns without congenital heart disease.

In the observed children, the main disease was somatic diseases, the exclusion criteria were patients with congenital malformations (except for congenital diseases of the cardiovascular system), prematurity, surgical diseases.

To determine the significance of risk factors, a questionnaire was compiled with a codifier of 42 signs reflecting socio-hygienic, medico-biological factors, the presence of intrauterine infections and medication intake by the mother during pregnancy and an obstetric and gynaecological history (tables 1-5)

In each figure, it is necessary to emphasize yes or no, in case of a doubtful answer, emphasize both answers. This questionnaire was filled out by the mother of the examined newborns, if necessary, we asked clarifying and additional questions, there were practically no difficulties in filling it out.

In order to obtain information and assess the risk factors of CHD, the "case-control" method was used. If this factor was present in a newborn with CHD, it was regarded as a "case", the fact of absence – as a "control" necessary to determine the differences in the effect of certain factors on the outcome of the observed or analyzed clinical phenomenon.

The studies were conducted using:

1. Epidemiological study of risk factors

2. Echocardiographic examination of the heart.

Statistical processing of the obtained results was carried out using the package of the statistical program "Statistica 6.0". The arithmetic means that its error and the Student's criterion were calculated. To determine the significance of the causes of the development of CHD, an information content analysis was carried out using the calculation of relative risk – RR and the calculation of the odds ratio OR with a 95% confidence interval. The value of the error probability (p-value) was calculated depending on the degree of freedom. The value of $P<0.05$ was considered reliable.

3 Results

Difficulties in assessing the significance of potential risk factors are also explained by the fact that to date there are few large prospective cohort studies on the study of biomedical, socio-hygienic or other impacts associated with congenital diseases of the cardiovascular system.

The results of the studies presented in Table 1 revealed a significant dependence of the frequency of heart disease on the age of a pregnant woman older than 35 years (OR 2.57), closely related (OR 4.69) and unregistered marriages (OR 4.48), which increases the risk of developing congenital anomalies. The significance of a closely related marriage can be explained by the influence of a hereditary factor on the development of congenital malformations and, of course, CHD.

Table 1. Analysis of socio-hygienic risk factors for the occurrence of congenital heart defects in newborn children according to the relative risk and odds ratio

№	Factors	Frequency (%)		RR	PS min RR	PS max RR	OR	PS min OR	PS max OR
		Total group n=324	Control group n=50						
1	higher education	20.1	26.0	0.95	0.85	1.06	0.71	0.36	1.42
2	Secondary education	79.9	76.0	1.03	0.93	1.15	1.26	0.62	2.54
3	the mothers' age is over 35 years old	25.9	12.0	1.10	1.03	1.19	2.57	1.06	6.24
4	the age of fathers is over 40 years old	21.0	18.0	1.02	0.93	1.12	1.21	0.56	2.61
5	professional harmfulness of mothers	7.1	2.0	1.11	1.01	1.22	3.74	0.49	28.36
6	bad habits of mothers	5.2	2.0	1.10	0.97	1.23	2.71	0.35	20.85
7	bad habits of fathers	9.0	6.0	1.05	0.93	1.18	1.54	0.45	5.26
8	closely related marriage	16.4	4.0	1.13	1.06	1.22	4.69	1.11	19.91
9	An unregistered marriage	15.7	4.0	1.13	1.05	1.21	4.48	1.06	19.03

Note: RR – relative risk, OR – odds ratio.

At the same time, the survey found that the remaining socio-hygienic risk factors for congenital heart defects in newborn children: higher and secondary education (OR 0.36 and 0.62), professional harmfulness of mothers (OR 1.74), bad habits of mothers (OR 1.71) and fathers (OR 1.54), the age of the father over 40 years (OR 1.21) did not have significantly significant differences in comparison with the control group. This made it possible not to include them in the group of modifying factors.

The analysis of biomedical risk factors (Table 2) revealed that the presence of CHD in the family (OR 7.70), severe anemia (OR 3.65) and acute upper respiratory tract infections in the mother during pregnancy (OR 3.98) showed a significantly higher incidence in patients with CHD compared to the control group.

Table 2. Analysis of biomedical risk factors for the occurrence of congenital heart defects in newborn children according to the relative risk and odds ratio.

№	Factors	Frequency (%)		RR	PS min RR	PS max RR	OR	PS min OR	PS max OR
		Total group n=324	Control group n=50						
10	CHD in the family	13.6	2.0	1.15	1.08	1.22	7.70	1.04	57.20
11	CVD in the family	5.6	2.0	1.10	0.98	1.23	2.88	0.38	22.08
12	hereditary diseases in the family	2.5	2.0	1.03	0.81	1.30	1.24	0.15	10.14
13	анемия средне-тяжелая форма	46.9	50.0	0.98	0.91	1.07	0.88	0.49	1.60
14	anemia is a medium-severe form	24.1	8.0	1.13	1.05	1.21	3.65	1.27	10.45
15	diabetes mellitus	2.2	2.0	1.01	0.78	1.32	1.08	0.13	8.99
16	obesity	3.7	4.0	0.99	0.80	1.23	0.92	0.20	4.25
17	Chronic foci of infection	8.3	14.0	0.91	0.76	1.08	0.56	0.23	1.36
18	exacerbations of chronic diseases	4.0	8.0	0.88	0.67	1.15	0.48	0.15	1.54
20	acute bacterial infectious diseases	8.3	12.0	0.94	0.80	1.11	0.67	0.26	1.71
21	acute upper respiratory tract infections	35.2	12.0	1.15	1.07	1.23	3.98	1.65	9.63
22	urogenital infection	3.7	6.0	0.92	0.71	1.19	0.60	0.16	2.21
23	gynecological infection	7.1	10.0	0.94	0.79	1.13	0.69	0.25	1.90

Note: RR – relative risk, OR – odds ratio.

The presence of CHD in the family undoubtedly indicates the significant role of hereditary factors, the severe degree of anemia that the mother has during pregnancy affects the development of the pathological process through the hypoxic genesis characteristic of anemia, and the role of acute upper respiratory tract infections during pregnancy, most often of a viral nature, is a generally accepted risk factor for congenital heart defects.

In the study, when assessing the relationship of congenital malformations in the family (OR 2.88), diseases suffered by the mother during pregnancy: moderate-severe anemia (OR 0.88), diabetes mellitus (OR 1.08), obesity (OR 0.92), the presence of chronic foci of infection (OR 0.56), exacerbation of chronic diseases (OR 0.56), acute bacterial infectious diseases (OR 0.67), urogenital (OR 0.60) and gynaecological infections (OR 0.69), indicates an unlikely influence of these data factors on the development of congenital heart defects. At the same time, it should be noted that most of these factors, such as urogenital or intrauterine infections in maternal diseases, have a bacterial genesis, which practically does not penetrate the uteroplacental barrier, thereby confirming the low significance of the study obtained.

Examination for the presence of herpetic viral infection during pregnancy in the mother (OR 48.8) as a factor causing CHD (Table 3), revealed a high diagnostic significance. Herpes infection, as one of the factors of the development of CHD, has previously attracted the attention of researchers [10]. due to its microstructure, due to which the infectious agent can penetrate the uteroplacental barrier to the fetus and have a negative impact on the formation of organs and systems, leading to the formation of various CVD, including defects of the cardiovascular system.

Table 3. Analysis of risk factors for the occurrence of intrauterine infections of the mother of congenital heart defects in newborn children according to the relative risk and the odds ratio

№	Factors	Frequency (%)		RR	PS min RR	PS max RR	OR	PS min OR	PS max OR
		Total group n=324	Control group n=50						
24	herpes	8,6	0,2	1,17	1,12	1,22	48,8	1,33	1,75
25	cytomegaly	4,3	6,0	0,95	0,76	1,19	0,71	0,20	2,56
26	chlamydia	7,1	4,0	1,07	0,94	1,21	1,83	0,42	8,03
27	toxoplasmosis	2,8	2,0	1,04	0,84	1,28	1,40	0,17	11,29

Note: RR – relative risk, OR – odds ratio.

At the same time, during the examination, it was found that cytomegalovirus (OR 0.71), chlamydia (OR 1.83) and toxoplasmosis (OR 1.28) infections during pregnancy in the mother were not significantly significant in comparison with the control group and were not factors causing CHD in newborns.

When analyzing the risk factors of taking medications by the mother during pregnancy for the occurrence of CHD in newborn children (Table 4), the only modifying factor was identified – the intake of antifungal drugs (OR 3.24), when children with CHD had a significant increase in their frequency in comparison with the control group.

Table 4. Analysis of risk factors for taking medications by a mother for the occurrence of congenital heart defects in newborn children according to the relative risk and the odds ratio.

№	Factors	Frequency (%)		RR	PS min RR	PS max RR	OR	PS min OR	PS max OR
		Total group n=324	Control group n=50						
28	antibiotics	92,0	84,0	1,15	0,95	1,39	2,18	0,93	5,14

29	non-steroidal anti-inflammatory drugs	62,0	78,0	0,91	0,85	0,98	0,46	0,23	0,93
30	antifungal	17,6	6,0	1,12	1,04	1,20	3,34	1,01	11,12
31	anticonvulsants	1,9	2,0	0,99	0,73	1,34	0,92	0,11	7,84
32	iron preparations	29,9	34,0	0,97	0,89	1,07	0,83	0,44	1,56
33	vitamins	19,4	18,0	1,01	0,92	1,12	1,10	0,51	2,38

Note: RR – relative risk, OR – odds ratio.

Taking other medications during pregnancy, such as antibiotics (OR 2.18), nonsteroidal anti-inflammatory drugs (OR 0.46), anticonvulsants (OR 0.92), iron preparations (OR 0.83) and vitamins (OR 1.10) did not have significant significance.

Numerous risk factors for the occurrence of CHD in newborns when analyzing the obstetric and gynecological history were (Table 5): the presence of miscarriages (OR 8.11), the threat of termination of pregnancy (OR 5.12), induced pregnancy (OR 5.68), severe toxicosis (OR 3.49), stress during pregnancy (OR 7.50) and fetal hypoxia (OR 4.01).

Table 5. Analysis of risk factors of obstetric and gynecological anamnesis of the occurrence of congenital heart defects in newborn children according to the relative risk and odds ratio

№	Factors	Frequency (%)		RR	PS min RR	PS max RR	OR	PS min OR	PS max OR
		Total group n=324	Control group n=50						
35	miscarriages	14,2	2,0	1,15	1,08	1,22	8,11	1,09	60,17
36	abortion	1,0	2,0	0,86	0,49	1,52	0,46	0,05	1,73
37	the threat of termination of pregnancy	17,6	4,0	1,14	1,07	1,22	5,12	1,21	21,69
38	induced pregnancy	19,1	4,0	1,15	1,07	1,22	5,68	1,34	24,00
39	multiple pregnancy	1,0	2,0	0,86	0,49	1,52	0,46	0,05	2,31
40	severe toxicosis	18,2	6,0	1,12	1,04	1,21	3,49	1,05	11,59
41	fetal hypoxia	20,4	6,0	1,13	1,05	1,21	4,01	1,21	13,28
42	stress during pregnancy	13,3	2,0	1,15	1,08	1,22	7,50	1,01	54,26

Note: RR – relative risk, OR – odds ratio.

The justification for the reliability of risk factors such as miscarriages, induced pregnancy is that organogenesis occurs during this period, and the causes of the development of these

pathological conditions lead to a violation of the formation of the fetus, including the cardiac and vascular systems.

The influence of hypoxia, as well as severe toxicosis, as one of the possible causes of CHD, is because when they are exposed during organogenesis, the death of the fetus or the development of the child occurs.

The presence of stressful situations during pregnancy undoubtedly has a negative impact, by disrupting metabolic processes, fetal blood circulation, arising during this process, on all possible stages of intrauterine development of the fetus, including the formation of organs of the cardiac and vascular systems.

The remaining risk factors of obstetric and gynecological history: abortions (OR 0.46) and multiple pregnancies (OR 0.46) were not significant factors for the development of CHD in the examined newborns.

4 Discussion

The current view of CHD risk factors recognizes their potential impact on the fetus, but their significance for specific reasons has not yet been fully determined. The causes of CHD are still not fully understood, as evidenced by the lack of a unified theory of the etiology of the disease.

There is a generally accepted opinion that the influence of environmental factors during the perinatal period and genotypic predisposition, as well as their combinations, have a dominant influence on the development of CHD [5, 15].

In recent years, there have been studies on the influence of various endo - and exogenous factors that are important for the formation of congenital malformations, including those of the heart with multifactorial genesis [16].

Difficulties in assessing the significance of potential risk factors are also explained by the fact that to date there are not enough published reports of large prospective cohort studies on the study of various effects associated with congenital diseases of the cardiovascular system.

One of the largest studies in the United States that have made a key contribution to understanding the causes and determining the risks for the birth of a child with birth defects is the National Birth Defects Prevention Study (NBDPS) project. To date, more than 200 scientific papers have been published using NBDPS data. Some examples of important findings: CHD is the most common type of birth defect, which affects about one in 100 children born in the United States. Most CHD occurs due to the complex relationship between the environment, lifestyle and genetic factors. Using genetic samples provided by the families, the NBDPS researchers identified changes in several genes. Variants in four genes were found to increase the risk of heart defects. This study is one of the first in NBDPS, in which the genes of infants and their mothers are studied [18].

There are reports that maternal diabetes, fever in the early stages of pregnancy is a reliable factor in the development of CHD, which was detected from 5% to 10% of women during the first trimester [11, 13].

According to Narcissova G. P., Volkova I. I., Lenko O. A., there is no significance between the age of a pregnant woman older than 35 years, the influence of in vitro fertilization and the probability of heart disease in the fetus. The probability of developing a fetal heart defect increases if a pregnant woman has acute respiratory viral, urogenital, intrauterine infections [6].

Saperova E. V., Vakhlova I. V. provides statistical data on the prevalence, analyzes the relationship with defects of other organs and systems, and the role of various factors in the formation of the risk of the disease in the fetus [17].

The study showed that the most significant risk factors for the development of CHD in the antenatal period are: tobacco smoking, exacerbation of chronic diseases, acute infectious

viral diseases in the first 6-8 weeks of pregnancy, cytomegalovirus infection, herpes virus infection and their combination, both in the acute and chronic stages of the infectious process [10].

In the study, the authors studied 2025,727 people born from 1978 to 2011, among whom there were 7296 (0.36%) mothers with pregestational and gestational diabetes mellitus, which significantly increases the risk of developing CHD, and conclude that the association of diabetes mellitus and CHD is possible with hyperglycemia up to 7 weeks of gestation [20].

In the conducted medical and sociological study, in the Altai Territory, in the families of 348 children with diagnosed CHD, it was shown that there were significantly unfavorable medical, material and living conditions. Of these, about 50.0% of children who suffered intrauterine hypoxia, were exposed to nicotine, viral infections [7].

When analyzing 162 medical histories of children with congenital heart defects treated in the cardiology department of the Amur Regional Children's Clinical Hospital, significant risk factors of the disease were established, such as anemia, chronic fetoplacental insufficiency, the threat of termination of pregnancy, toxicosis of the first half of pregnancy and acute viral infection suffered in the early stages of pregnancy [4].

Saatova G. M., Furtikova A. B., Zhanturaeva B. T. revealed that the structure of risk factors for the formation of CHD in the fetus is dominated by medical, environmental, social and biological predictors are less significant when studying 80 families with children with CHD in Kyrgyzstan [8].

An analysis was carried out, which revealed that the age of the father, an unfavorable obstetric history, antenatal fever and the elderly age of the mother (OR, 3.28) increase the risk of CHD [12].

At the same time, the authors consider the need for further research in this direction [13].

5 Conclusion

The study of the problem of CHD in newborns undoubtedly indicates a significant contribution of endogenous and exogenous factors in the formation of the disease.

An analysis of the latest global studies to identify a reliable link between the influence of certain factors in pregnant women on the risk of developing CHD in a newborn shows the ambiguity of data, the solution of which will improve the quality of life of patients.

In our study, the identified risk factors for the development of CHD in newborns were somewhat similar to previous studies.

Thus, the analysis of the relative risk indicators and the odds ratio in newborns of the main and control groups allows us to conclude that the modifying risk factors for the development of congenital heart defects in newborns are: the mother's age over 35 years, closely related and unregistered marriage, congenital heart defects in the family, the presence of severe anemia during pregnancy in the mother, acute upper respiratory tract infections, herpetic viral infection, taking antifungal drugs, miscarriages, the threat of termination and induced pregnancy, stressful situations, severe toxicosis and fetal hypoxia.

Thus, the presence of these factors in the mother during pregnancy puts their newborns at risk of congenital heart defects, which will allow planning the optimal timing and methods of treatment, as well as prevention of the disease.

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